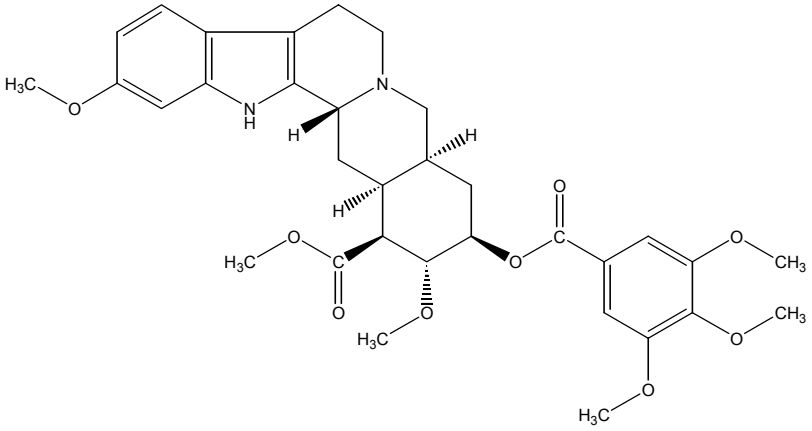
RESERPINE
CAS No. 50-55-5
First Listed in the *Second Annual Report on Carcinogens*



CARCINOGENICITY

Reserpine is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in experimental animals (NCI 193, 1980). When administered in the diet, reserpine increased the incidence of adrenal medullary pheochromocytomas in male rats and mammary adenocarcinomas in female mice and induced undifferentiated carcinomas of the seminal vesicles in male mice. When administered by subcutaneous injection, reserpine slightly increased adrenal pheochromocytomas in rats and mammary neoplasms in mice. IARC Working Groups considered that the evidence for the carcinogenicity of reserpine in experimental animals was limited (IARC V.24, 1980; IARC S.4, 1982; IARC S.7, 1987).

There are no data available to evaluate the carcinogenicity of reserpine in humans. The available evidence relating exposure to reserpine with breast cancer is not consistent, between and within studies (IARC S.4, 1982; IARC S.7, 1987). An earlier Working Group considered the evidence from case-control and cohort studies to be limited and indicated that a small increase in the risk of breast cancer development could not be ruled out (IARC V.24, 1980).

PROPERTIES

Reserpine occurs as white or slightly yellow crystals or crystalline powder. It is practically insoluble in water; slightly soluble in acetate, methanol, ethanol, diethyl ether, and aqueous solutions of acetic and citric acids; and soluble in chloroform, dichloromethane, glacial acetic acid, benzene, and ethyl acetate. Reserpine is sensitive to oxidation and hydrolysis. The compound acquires a yellow color with pronounced fluorescence, especially after the addition of acid or exposure to light. When heated to decomposition, it emits toxic fumes of nitrogen oxides (NO_x). Reserpine is available in the United States as a USP grade containing 97-101% active ingredient on a dried basis. The product may be contaminated with alkaloids, such as rescinnamine, which may co-exist with reserpine in *Rauwolfia* species. Commercial formulations have been marketed under approximately 221 trade names.

USE

Reserpine is a naturally occurring alkaloid produced by several members of the genus *Rauwolfia*, a climbing shrub indigenous to southern and southeast Asia. The compound is used primarily as a peripheral antihypertensive and as a central depressant and sedative. It is used alone or in combination with thiazide diuretics for the management of mild labile hypertension and in conjunction with potent hypotensive agents for the management of essential hypertension and hypertension associated with toxemia in pregnancy. Reserpine has been used as a sedative for mild anxiety and chronic psychoses but is rarely used for this purpose now. Reserpine has also been used in poultry feeds as a sedative and to prevent aortic rupture in turkeys (IARC V.10, 1980; IARC S.4, 1982). It has also found use as a radioprotective agent and experimentally as a contraceptive (Kirk-Othmer V.16, 1979; Kirk-Othmer V.19, 1983). Extracts of *Rauwolfia serpentina* have been used medicinally in India for centuries. They were used in primitive Hindu medicine for a variety of conditions, including snakebite, hypertension, insomnia, and insanity (IARC V.10, 1976; IARC V.24, 1980).

PRODUCTION

The Chem Sources International directory identified two suppliers and one bulk producer/supplier of reserpine and one supplier of *Rauwolfia serpentina* for 1988-1989 (Chem Sources, 1988). The Chem Sources USA directory identified 2 producers and 23 suppliers of reserpine and 3 suppliers of *Rauwolfia serpentina* and 1 supplier of *Rauwolfia vomitoria* extract (Chem Sources, 1986). Production volumes are not currently available. There is no known commercial production of synthetic reserpine, although it has been marketed (IARC V.10, 1976; IARC V.24, 1980). In 1983, the United States imported 103 lb of reserpine (USITCa, 1984). The 1979 TSCA Inventory identified one producer of reserpine in 1977, but no production volume was reported (TSCA, 1979). No data on exports are available. U.S. sales of reserpine dropped 50% from 1976 through 1979, indicating a reduction in reserpine use. Annual U.S. sales of reserpine for use in human medicine were about 440,000 lb in 1976.

EXPOSURE

The primary routes of potential human exposure to reserpine are inhalation, injection, ingestion, and dermal contact. In soil or water adsorption and ionization will occur. Since the compound is extracted by only two domestic companies, the potential for exposure during production is limited. However, since there are several suppliers of reserpine, there is a risk of exposure during the formulation and packaging of pharmaceuticals containing the compound. The National Occupational Exposure Survey (1981-1983) indicated that 5,516 workers, including 2,344 women, potentially were exposed to reserpine (NIOSH, 1984). This estimate was derived from observations of the actual use of the compound (97% of total observations) and the use of trade name products known to contain the compound (3%). Health professionals such as doctors, nurses, and pharmacists, may be potentially exposed while dispensing, preparing, or administering the pharmaceuticals to patients with hypertension or high blood pressure. Patients actually receiving the drug are exposed to doses of 0.25 mg three to four times daily for 2 weeks for control of moderate hypertension; the dosage is then reduced to the lowest necessary to maintain the response. Children may be given 20 µg/kg body weight daily in divided doses. For hypertensive crises, an intramuscular injection of 0.5-1.0 mg is administered; if there is no significant fall in blood pressure in 3 hr, 2-4 mg are injected at 3- to 12-hr intervals until the pressure falls to the desired level (IARC V.24, 1980). In 1979, retail pharmacies dispensed about 15.7 million prescriptions for reserpine, and hospitals dispensed an additional 2.3 million

prescriptions. It was estimated that one million Americans were using reserpine to control high blood pressure in 1979. In 1974, FDA estimated that four million people in the United States were using reserpine formulations. The general population may have been exposed to reserpine in chickens and turkeys fed reserpine-containing diets.

REGULATIONS

Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), EPA has established a reportable quantity (RQ) for reserpine of 5,000 lb. Reserpine is regulated as a hazardous constituent of waste under the Resource Conservation and Recovery Act (RCRA). FDA regulates reserpine as a prescription drug approved for human use and formerly regulated its use in animal diets. FDA has revoked the use of reserpine as a component of premixed turkey feed. OSHA regulates reserpine under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-131.